## ABSTRACT

**Purpose:** Most veterans live for many years after their war-related traumatic lower-limb amputation, which is why understanding which factors influence health-related quality of life (HRQoL) remains important to their long-term management. The objective of this study was to perform a review of the literature to summarise any evidence on the physical and social determinants for HRQoL in veterans with uni- or bilateral lower-limb amputation(s).

**Method:** MEDLINE, EMBASE, PEDro, CINAHL, Scopus and Cochrane databases were searched systematically for eligible studies. Inclusion criteria were: traumatic lower-limb amputation(s), HRQoL outcome and veterans. Physical and social factors that influence HRQoL were extracted.

**Results:** The literature search identified 2073 citations, leading to the inclusion of ten studies in the systematic review. Physical activity level, sport participation, level of amputation, back pain, years of education, as well as duration and severity of phantom pain were found to be determining factors for HRQoL among veterans with lower-limb amputation.

**Conclusions:** The identified physical and social determinants were similar to those found in civilian traumatic amputees. More high quality research designs, interventions and complex statistical analyses are warranted to identify the physical and social factors that influence the HRQoL of veteran amputees.

## INTRODUCTION

In 2005 an estimated 1.6 million people lived with the loss of a limb in the USA and at the end of 2013 there were 1,558 traumatic war-related amputations registered due to military operations in Iraq and Afghanistan [1,2]. A twenty-four-year follow-up study on veteran amputees with traumatic lower-limb amputations revealed increased mortality rates compared to the general population (21.9% vs. 12.1%) [3]. Many veteran amputees, however, live for many years after their war-related traumatic lower-limb amputation [3], highlighting the importance of understanding the quality of life (QoL) of survivors. Health-related quality of life (HRQoL) reflects an overall sense of well being comprising the emotional, physical and social aspects of a person's life [4]. HRQoL after amputation is therefore an important short- and long-term outcome measurement for patients with lower-limb amputations [5].

Veterans with lower-limb amputations due to war-related activities are typically young men in good physical shape with a military mind-set. Therefore, the underlying physical and social determinants of HRQoL may differ in veteran amputees compared to civilians. Identification of specific determinants in veterans with traumatic amputation(s) may provide crucial information for planning rehabilitation interventions for veterans with lower-limb amputation(s). Even though HRQoL is an important and relevant outcome, not much is known about the underlying physical and social factors that influence HRQoL in veterans with lower-limb amputation. Both vascular and traumatic lower-limb amputees showed decreased HRQoL [6-9], the determining factors being: increasing age [9-11], higher unemployment [9], more phantom pain [9, 12], more residual limb pain [9-11], higher depression levels [10] and lower physical function [10-13], but these findings are not specific for veteran amputees.

48 It is unknown whether the above-mentioned determinants are the same for veteran
49 amputees. As a result, the objective of this study was to systematically review the
50 literature concerning the relationship between physical and social determinants and
51 HRQoL in veterans with uni- or bilateral lower-limb amputation(s).

## Methods

### Protocol and registration

After initially screening a large volume of studies for relevance and eligibility, we registered and published a protocol for our systematic review in PROSPERO, an international database of prospectively registered systematic reviews in health and social care, no. CRD42014014437.

### Eligibility criteria

To be included in our review studies had to examine veterans with uni- or bilateral transtibial, knee joint, transfemoral, hip joint or trough pelvic bone amputation(s) [14] and they had to study HRQoL factors. Randomised controlled trials, quasi-randomised controlled trials, controlled trials, cohort studies, and cross-sectional studies were accepted. No language, publication date or publication status restrictions were imposed.

### Search

The following databases were searched on 28 September 2014: National Library of Medicine (MEDLINE), Physiotherapy Evidence Database (PEDro), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica dataBASE (EMBASE), Scopus, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effect. The search matrix consisted of a combination of lower-limb amputation and veterans, with synonyms and indexed terms. Supplementary Table S1 provides an

example of a search matrix used in MEDLINE. Reference lists in the studies identified were also screened to include any additional studies of relevance.

**Study selection**

First, two reviewers (JC, TI) independently screened for eligible studies by title and abstract. Next, the eligible studies were compared and differing opinions discussed. Finally, the two reviewers independently performed the process again on full text articles.

**Data collection process**

JC and TI extracted data from the trials independently. A standardised form was used to collect descriptive data on the study populations, level of amputation, inclusion criteria, time since amputation and physical and social factors for HRQoL. Data and figures were crosschecked.

**Assessment of risk of bias in individual studies**

The National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to rate the methodological strength and risk of bias for the eligible studies [15]. The two reviewers discussed any disagreements concerning the study selection process, including bias, to reach consensus. A third reviewer arbitrated where necessary.

**Quality of evidence**

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) was used to assess the overall quality of evidence [16] based on the following five

101 factors: risk of bias, indirectness, inconsistency, imprecision and publication bias. The
102 body of evidence identified for each outcome was rated as high, moderate, low or
103 very low quality.

## RESULTS

### Study selection

The literature search identified 2073 citations, 1005 of which were duplicates (figure 1). The remaining 1068 unique articles were screened for eligibility by title and abstract, resulting in 29 potential articles for full-text review, 23 of which were excluded. During the full-text reading an additional two studies were identified and included after undergoing the same selection process (Dougherty 1999, 2001), resulting in ten articles for our systematic review. Supplementary Table S2 lists the characteristics of the studies that were excluded.

*Insert figure 1 about here*

### Synthesis of results

A descriptive analysis of the data was undertaken due to the heterogeneity of the studies. Physical and social factors that influence HRQOL will be presented separately.

### Characteristics of included studies

Table 1 presents the title, design, participants, inclusion criteria, primary outcome, and main findings of the included studies.

*Insert table 1 about here*

## Quality assessment and risk of bias in included studies

Figure 2 shows the quality assessment and risk of bias summary of the included studies.

*Insert figure 2 about here*

## Factors influencing HRQoL

Ten cross-sectional studies investigating determining factors for HRQoL were included and divided into three groups: Studies directly investigating determinants of HRQoL, studies comparing veterans to the normal population and studies comparing veterans to other veterans.

*Studies directly investigating determinants of HRQoL*

Two studies investigated the factors that influence HRQoL[17, 18]. A significant negative relationship was found between severity of phantom pain and three Short Form-36 Healthy Survey (SF-36) domains: physical functioning, general health and physical component scale [17]. No R or R-squared values for the correlations of variability were stated. Findings also showed a significant negative relationship between duration of phantom pain and physical functioning, bodily pain, mental health and physical component scale. Furthermore, 61% of the amputees reported vertebral column pain. The presence of either vertebral pain or neck pain was significantly associated with lower scores on the subscales for bodily pain, vitality, social functioning, mental health, physical component scale and mental component scale [17].

Participants who suffered from thoracic pain had significantly lower scores on the

152 physical function subscale, general health, vitality, social function, mental health,
153 physical component scale and mental component scale [17].
154 In another study, poor physical HRQoL was positively associated with the presence of
155 phantom movement, low back pain, transfemoral amputation and a lower Barthel
156 Index score [18]. No R or R-squared values for the correlations of variability were
157 stated. Amputees who had received educational services represented a higher
158 percentage of veterans with a good physical HRQoL (40 cases, 87.0%) compared
159 with others (66 cases, 69.5%), (*p=0.02*). Likewise, a good mental HRQoL was
160 significantly higher among veterans who received additional education (41 cases,
161 89.1%) compared to those who had not since the amputation (65 cases, 68.4%),
162 (*p=0.01*).

163 *Studies comparing veterans to the normal population*
164 Two studies compared veteran amputees to a normal population [19, 20].
165 Significant between-groups differences were found on the SF-36 subscale physical
166 functioning, with no differences observed on any other subscales [19]. Forty-three
167 percent of the veterans reported still walking, 78% used a wheelchair as primary
168 transportation, 70% were employed and 91% were married. No determining factors
169 were reported.
170 Significant between-group differences on all SF-36 subscales were reported for
171 amputees with an additional major long-bone fracture of the lower extremity, burns
172 covering >20% of the body, or a chest, abdominal, face or head wound, compared to
173 the normal population [20]. All amputees with additional injury were employed, 93%
174 were married, 82% had children and 21% received psychological care. For the group
175 of amputees without an additional injury no significant between-group difference was
176 observed when compared to the normal population. Ninety-eight percent of the

177 amputees without additional injury were employed and married, 84% had children
178 and 50% received psychological care. No determining factors were reported in either
179 of the two groups.
180
181 *Studies comparing veterans to other veterans*
182 Six studies compared veteran amputees to another veteran population [21-26].
183 No differences in the prevalence of depression, posttraumatic stress disorder and brain
184 injury were found between groups or type of limb loss, but an increasing prevalence
185 of chronic back pain with more limbs amputated was found [21, 22].
186 Patients from the Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF)
187 group had a better function compared to the Vietnam War group [22]. Employment was
188 reported as 77% for the Vietnam War group and 60% for the OIF/OEF group. No
189 significant difference in HRQoL was observed between groups, but 55% of patients in
190 the Vietnam group rated their HRQoL as excellent/very good while 70% in the
191 OIF/OEF group did.
192 The OIF/OEF group had a higher level of function, four out of eleven reporting
193 participation in high-impact activities versus none in the Vietnam War group
194 ($p=0.018$) [23]. QoL was similar between groups, with excellent, very good and good
195 QoL reported for 69% of the Vietnam War group and 73% of the OIF/OEF group
196 ($p=0.85$). Other health factors were non-significant.
197 In another study the OIF/OEF group reported better QoL compared to the Vietnam
198 War group [24]. Those with unilateral lower-limb loss reported their amputation had the
199 highest effect on their current life (amputation impact rank = 7.5 ±2.7, $p<0.05$)
200 compared with multiple limb loss (7.1 ±3.1).

For those with unilateral lower-limb loss in the Vietnam War group, the highest effect for injury to the non-amputated lower limb (mean combat injury rank = 5.4 ±3.1) [24]. There was no difference in self-reported health status among veterans with lower-limb amputations as 81.9% in the Vietnam War group and 84.8% in the OIF/OEF group reported excellent to good health [25]. In the OIF/OEF group, 52% were significantly more likely to do low- and high-impact activities compared 20% in the Vietnam War group. No difference was observed between groups regarding total pain but mental health was worse in the OIF/OEF group.

Veterans who participated in sports had higher favourable physical subscale scores on SF-36 [26]. Furthermore, veterans with more proximal amputations remained more symptomatic (e.g. phantom sensation and phantom pain). Overall, 93% of veterans were married and 90% reported back pain.

**Quality of evidence and risk of bias across studies**

As stated in the protocol and the methods section the present review aimed to include randomised controlled trials, quasi-randomised controlled trials, controlled trials, cohort studies and cross-sectional studies; however, due to limited evidence base only cross-sectional studies were included in this systematic review.

GRADE was used to evaluate the quality of the body of evidence for determining factors for HRQoL. Only two of the included studies were designed to directly investigate factors determining HRQoL; however, when data was available, relevant factors for HRQoL were included in the present review. All of the included studies were cross sectional and the majority of them had relatively small sample sizes, which means publication bias cannot be assessed or ruled out. Results varied considerably concerning physical activity, some studies identifying it as a determining factor for

HRQoL and others failing to find a relationship between the two. The authors of the present review rate the body of evidence to be of very low quality for each of the identified determinants for HRQoL among veterans with lower-limb amputation(s). Table 2 presents the individual ratings in a GRADE profile.

*Insert table 2 about here*

## DISCUSSION

### Summary factors that influence HRQoL

The identified HRQoL determinants for veteran amputees included: higher physical activity, years of education, higher phantom pain severity, duration of phantom pain, level of amputation and back pain.

Higher physical activity level and years of education were positively associated with better physical and mental HRQoL [17].

Higher phantom pain severity is a predictor of lower scores on SF-36 subscales for physical functioning, general health and for the physical component scale [17]. Phantom pain is often reported to be a determining factor for HRQoL and veteran amputees with phantom pain have poorer HRQoL compared to civilian amputees without phantom pain [12, 27]. For veteran amputees, the duration of phantom pain is associated with worse physical functioning, bodily pain, mental health and a lower score on the physical component scale [17]. Higher proximal level of amputation is associated with more bodily pain [26] and lower HRQoL [18, 20].

Civilians with lower-limb amputation(s) often report back pain[17, 18, 28-30]. For veterans with lower-limb amputation(s), back pain is associated with lower scores on the subscales for bodily pain, vitality, social functioning, mental health and on the physical component and mental component scales [17]. Furthermore, back pain is associated with poor physical HRQoL[18].

This systematic review only included studies that examined veterans with lower-limb amputation(s). This group is primarily younger men in relatively good physical shape before the amputation. With this in mind, the authors did not hypothesise that a civilian population necessarily would have the same determining factors for HRQoL as veterans. Nevertheless, many of the factors identified in this present review were

not unique to the veteran amputee as they were likewise reported among civilian amputees. These more general determinants include: age, number of comorbidities, level of amputation, time since amputation, residual stump pain, phantom limb pain, social support, employment status and depressive symptoms [9, 10].

It was not possible to state how much of the variation in HRQoL was due to the identified factors. Neither $R$ nor $R^2$ was reported in the studies included in the present review. For civilian amputees the eight known determinants: age, time since amputation, phantom limb pain, employment status, use of prosthesis, comorbidities, use of assistive devices and residual limb pain explained up to 50.8% of the variance observed in physical HRQoL [9]. Depression in civilian patients accounted for 30% of the variance observed in HRQoL, with six other factors accounting for an additional 18% of the observed variance [10].

Due to poor reporting in the ten eligible studies, this review was unable confidently quantify the extent of contribution for most of the identified factors for veterans. Generally, the included studies had small sample sizes, some did not provide long-term outcomes and all of them showed shortcomings in the methodological quality, not to mention a medium to high risk of bias. Based on GRADE, the quality of evidence for each of the identified determinants is very low due to the study design, indirectness of the research question in some of the studies, the inconsistency of findings between studies and due to the probability of publication bias, table 2. Notwithstanding the above findings, the very low grade reflects that the authors suspect that the determinants identified in the studies may vary substantially from the ones identified in the current review. Good methodological studies with larger sample sizes are urgently needed to better understand the factors that influence HRQoL in veterans with lower-limb amputation.

## Limitations

The findings in this review are limited to veterans with traumatic lower-limb loss. The review included studies that did not primarily focus on factors that influence HRQoL. As a result, some factors that affect HRQoL may have been ignored and data unreported in those articles. Because the total body of evidence was not very large, we nonetheless included these studies to obtain the data that was available on the reported determinants

Two of the studies in the present review were conducted over ten years ago and may not reflect modern service provision and outcomes. In recent years prosthetics have improved, which has possibly had an impact on HRQoL.

Used to assess the quality and risk of bias in the studies in this review, the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies is based on a subjective assessment but bolstered by NIH guidelines and supplemented by an evaluation based on consensus.

## CONCLUSIONS

### Implications for practice

This systematic review identified physical activity level, sport participation, level of amputation, back pain, years of education, as well as duration and severity of phantom pain as determining factors for HRQoL among veterans with lower-limb amputation. When considering interventions aimed at improving HRQoL, clinical and rehabilitation teams are well placed to promote physical activity and sport but should also take into account the level of amputation, the extent of back pain and the severity of phantom pain.

*Insert Implication for Rehabilitation Box about here*

### Implications for research

A key recommendation from this review is that HRQoL studies involving veterans should adopt a higher level of reporting for correlation and regression analyses. Systematic reviews are only as good as the data they collate and the study types they include, which suggest that more high quality research designs, interventions and complex statistical analyses are warranted to identify which physical and social factors influence HRQoL.

### Future research

As a result of the involvement in Iraq and Afghanistan, health care systems are facing long-term future challenges in caring for veterans [31]. To manage these challenges, there is an urgent need to identify and study the factors that influence HRQoL to be able to meet veterans' rehabilitation needs and to prevent the increased mortality rate among veterans due to cardiovascular disease [3, 32]. For example, clinical trials can

play a part in determining the effectiveness of interventions aimed at improving HRQoL, while registry and audit data sets can help determine if routine practices in amputee centres produce the desired effects.

## Declaration of interest

The authors declare no conflict of interest. This study was funded by the Danish Defence Agreement 2013-2017.

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## TABLE AND FIGURE CAPTIONS

**Figure 1:** Flowchart showing systematic literature search, screening of studies, full text reading, and studies included in review with number and reasons of study exclusion at each stage.

**Figure 2:** Quality assessment and risk of bias summary based on the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies": review authors' judgements about quality assessment and risk of bias for each included study.

**Table 1:** Characteristics of included studies

**Table 2:** GRADE profile for Health Related Quality of Life determinants